Central Estimates of Risk at Low Doses: Issues and Approaches

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1. Introduction

Policy analysts often need expected values of estimated risk to compare with expected values of regulatory costs. If one has a situation where the probability distribution of estimates of risk is not symmetrical, the maximum likelihood estimate (MLE) might be very different from an expected value estimate of risk and might be misleading. According to statistical theory, MLE could have undesirable properties when the estimate approaches a boundary. When this happens, the MLE of the linear coefficient of a multistage model is extremely unstable, and can predict risks ranging in several orders of magnitude with a slight change of data. Therefore, an alternative central estimate is needed.

We propose two related procedures that lead to central estimates of risk in the multistage model. The procedures are illustrated by examples. In the examples, we assume that multistage model holds.

2. Proposed estimates of risk

Bayesian estimate

At low doses:

$$Ave(ExcessRisk(d)) \approx Ave(q_1) * d = \frac{\int \ldots \int q_1 L(q_0, \ldots q_k) dq_0 \ldots dq_k}{\int \ldots \int L(q_0 \ldots q_k) dq_0 \ldots dq_k} * d$$

Where $L(q_0, q_1, \ldots q_k)$ is the likelihood function for the parameters, $q_0, q_1, \ldots q_k$, in multistage model

We use Markov Chains Monte Carlo software to simulate posterior distribution of the risk.

Bootstrap based estimate

The two-step procedure is proposed. In the first step, Bayesian estimates of probabilities of tumor are obtained from the observed data. Then, obtained probabilities are used for parametric bootstrap of the dose-response curve. For each simulation, the MLE of risk is generated and distribution of the risk is obtained.

3. Example of MLE stability. Naphthalene

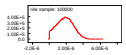
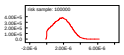
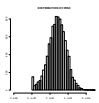
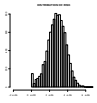
Dose	Original data	One tumor moved
0	0/49	0/49
10	6/49	7/49
30	8/48	8/48
60	15/48	14/48
MLE risk	3.5E-6	3.5E-6
95th risk	5.6E-6	5.7E-6

In this example, the MLE is stable and doesn't change much when data on number of tumors is somewhat changed. The estimate of upper 95th percentile is also quite stable and close to the MLE.

In all examples, the number of stages in the multistage model equal number of doses minus one.

Naphthalene: respiratory epithelial adenoma (REA) in male rats (Abdo et. al. 2001) Risk at .0005ppm

4. Naphthalene: REA in male rates

	Original data	One tumor moved
Bayesian estimate		
Estimate of expected risk	1.9E-6	1.8E-6
95th Confidence limit	3.4E-6	3.5E-6
Bootstrap estimate		
Estimate of expected risk	2.9E-6	2.8E-6
95th Confidence limit	4.5E-6	4.5E-6

Both strategies provide stable results very close to the MLE and to the upper 95th confidence limit

5. Example of MLE instability Simulated data

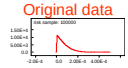
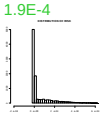
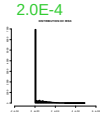
Dose	Original data	One tumor moved
0	0/50	0/50
1	10/50	10/50
1.46	23/50	24/50
2.02	42/50	41/50
MLE risk	2.1E-10	1.8E-5
95th risk	1.8E-4	2.1E-4

When MLE of linear term is equal to zero (left column), the MLE risk is not stable. It changes 5 orders of magnitude when just one animal is moved between two tumor groups.

Even when MLE risk is not near zero (right column), it can be unstable. The proposed strategies allow identifying such cases.

Simulated data with risk at .001ppm

6. Simulated data example

	Original data	One tumor moved
Bayesian estimate		
Estimate of expected risk	6.9E-5	7.0E-5
95th Confidence limit	1.9E-4	2.0E-4
Bootstrap estimate		
Estimate of expected risk	2.9E-5	3.1E-5
95th Confidence limit	1.5E-4	1.7E-4

Both strategies provide stable results and close estimates

7. Example of MLE instability Formaldehyde

Dose	Original data	One tumor moved
0	0/341	0/341
0.07	0/107	0/107
2	0/353	1/353
6.01	3/343	3/343
9.93	22/103	22/103
15	162/386	161/386
MLE risk	4.5E-14	4.5E-7
95th risk	4.1E-6	9.4E-6

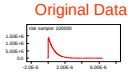
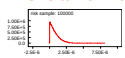
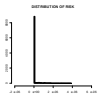
Risk at .001ppm

The MLE risk is not stable in the example from the actual animal experiment (formaldehyde). It changes 5 orders of magnitude when just one animal is moved between tumor groups.

Even when MLE is not near zero (last column), we cannot be sure that it is stable.

Formaldehyde: Squamous cell carcinoma (SCC) in rats (Kerns et al. (1983), Monticello et al. (1996))

8. Formaldehyde: SCC in rats

	Original Data	One tumor moved
Bayesian estimate		
Estimate of expected risk	6.4E-7	8.5E-7
95th Confidence limit	1.9E-6	2.3E-6
Bootstrap estimate		
Estimate of expected risk	8.6E-8	2.3E-7
95th Confidence limit	6.6E-7	1.7E-6

Bayesian methodology produces a more stable estimate for this example of a quite steep dose-response relationship.

9. Discussion and Future Work

- The examples demonstrate that both strategies produce distribution of risk and allow the derivation of central (expected) estimates of risk.
- Additionally, the shape of the distribution can be used to identify cases when MLE is unstable despite not being close to zero.
- Both approaches provide distributions of risk that could, after further development and review, be used in cost-benefit analysis.
- Both estimates of expected risk are generally stable against changes that cause point MLE of risk to jump several orders of magnitude. However, Bayesian estimates seem to be advantageous when shape of dose-response is very steep.

Next step would be to obtain distribution and central estimates of risk for time-to-tumor models. The Bayesian approach is more appropriate for extension to time-to-tumor, but some issues remain to be solved.